# Desmopressin Acetate Effects on Human Vigilance Task and Psychomotor Performances in Normal Healthy Volunteers: Randomized Single Blind Clinical Trail

**Hayder M. Al-Kuraishy MBChB, MSc***

**Abstract**

**Background**: Desmopressin is a synthetic form of human vasopressin hormone act chiefly on $V_2$ receptor that found in vascular and brain tissues ;and it's primarily used for treatment of nocturnal enuresis .Also previous studies in animals suggested that central vasopressinergic system proceed on cognitive function .

**Aim of study**: This study aimed to estimate the central effects of desmopressin on human vigilance task and psychomotor performances in normal healthy volunteers.

**Subjects and method** : This study done in the course of measurement of recognition reaction time (RRT); movement reaction time (MRT),total reaction time(TRT) and flickering-fusion frequency threshold which reflects the vigilance task and psychomotor performances by specific Leeds Battery Instrument before and after single trans-nasal desmopressin acetate in 20 healthy volunteers(17 males+3 females).

**Results:** This study showed that desmopressin produced significant effects on all vigilance- psychomotor performance parameters ($P$<0.05) with the exception of on critical flickering which produced insignificant effects ( $P$ >0.05).

**Conclusion**: Desmopressin acetate significantly improves human vigilance- psychomotor performances and improves cognitive function so we recommend using this drug for nootropic effects and stimulation of mental function.

**Key word**: desmopressin; psychomotor performance and critical flickering.

## INTRODUCTION

Desmopressin is a modified form of the normal human arginine vasopressin hormone (AVP).

In addition, it has little effect on blood pressure, while vasopressin may cause hypertension, desmopressin acetate is a long-acting synthetic analog of vasopressin with minimal $V_1$ activity and an antidiuretic-to-pressor ratio 4000/1 times that of vasopressin ,desmopressin can be administered intravenously, subcutaneously, intranasal, or orally, the half-life of circulating desmopressin is 1.5–2.5 hours[1].

Direct effects of AVP on central nervous system (CNS) function did not materialize until, DeWied study that verified removal of the posterior and intermediate lobes of the pituitary accelerate extermination of avoidance behavior in rats without affecting its achievement, an effect that could be normalized by peripheral administration of crude pituitary extract or lysine vasopressin (LVP) [2].

Subsequent research showed that AVP actions in the CNS has broaden to include other behaviors (e.g. social, reproductive and rewarded effects), in addition to the regulation of circadian rhythms and autonomic functions. Central vasopressinergic system is functionally and physiologically separate from the classic endocrine roles established for AVP released into peripheral circulation [3].

The central vasopressinergic system refers to the sites of synthesis and release of AVP within the CNS, where AVP acts as a neuromodulator and neurotransmitter this called extra-hypothalamic site[4].

The extra -hypothalamic sites are intermediate and medial subdivisions of the amygdaloid nucleus, which form vasopressinergic innervations throughout the CNS [5]. Expression of AVP in this site is dependent on sex steroids, with males exhibiting more relative to females [6].

The biological activity of AVP is mediated through group of receptors these are V1R (vascular vasopressin receptor) it is widely expressed among peripheral tissues (liver, vascular smooth muscle, kidney, spleen, testis and CNS) V2R (renal vasopressin receptor) strong expression of V2R is also observed in the epithelial cells and vascular endothelial cells of the choroid plexus, V3R (pituitary AVP receptor) at corticotrophs of the anterior pituitary other AVP receptors called dual angiotensin/AVP receptor their function are unknown [7'8'9].

AVP has special effects on reaction time and learning, systemic administration of AVP delays disappearance of avoidance response in rats, while central administration of the AVP receptor antagonist produced an opposite reaction [10]. Memory recovery, measured by retention-test performance is enhanced by pre-treatment with lysine vasopressin (LVP), and inhibited by the AVP receptor antagonist [11]. AVP is also implicated in awareness and dose dependent facilitation of learning and working memory in the task [12].

Moreover; AVP facilitated acquisition and lessened the reversal of learning and enhancement of cognitive functions such as learning this effects is not mediated through direct actions of AVP on CNS activity, but indirectly through changes in the motivational and arousal processes of animals[13].

Many objective laboratory tests are commonly used to evaluate the effect of drugs on different higher cortical functions, motor capacity, coordination and sensory capacity. these are Recognition Reaction Time (RRT), this test internationally evaluates psychomotor performance, measurement is made of the time taken to recognize the stimulus (simple reaction time), and of motor response velocity (complex reaction time), in milliseconds, in the course of 5consecutive attempts; Critical flicker fusion (CFF) this test measures alertness and central integration task functions, the subject defines the frequency required for a sequence of blinking lights to remain fixed or unremitting .Total Reaction Time(TRT) this test measures

parameters such as coherence or exactness in adjusting to speed. [14'15].

Human psychomotor performance reflects, the time a subject takes to react to a single or more stimuli, but there is only one correct response; depending on the response which may be simple or complex reaction time[16]. The reaction time for motor perception and response was the same in all types of reaction time, implying that the differences in the psychomotor performance are due to processing time, which is the time needed to recognize the meaning of sensation from memory to interpret the signal input[17].

The critical flickering and fusion frequency (CFF) measure the cognitive functions and it either descending, measure the time needed for perception of light from steady to flickering state while, ascending measure the time needed for perception of light form flickering to steady state[18,19].

The aim of this study is to evaluate of desmopressin acetate effects on psychomotor performances on normal healthy volunteers.

## Subjects and Methods

This study was carried in Department of Pharmacology, College of Medicine, Al-Mustansiriya University, Baghdad-Iraq, during April of 2011. It is approved by the scientific Jury of Department of Pharmacology and qualified by the parquet of Medical College. The subjects of this study were medical college students. 20 volunteers (17 males and 3 females) were accepted to enroll and complete this single blind random clinical study.

Each subject is asked to do the following procedure under the supervision. These tests were performed before trans-nasal administration of desmopressin acetate considered as baseline data of psychomotor performance and, immediately after 2.5h of dessmopressin nasal spray 0.1mg/ml desmopressin acetate (Minirin; Ferring pharmaceuticals; Istanbul 10µg/puff).

The principle of this test is to respond to the illuminated a bright red color light, by press the button. Therefore, the time needed for stimulus to be recognized is called recognition reaction time (RRT) which represents the time from stimulus onset to the beginning of motor action. And the time from onset of motor action to the end of performance called movement reaction time (MRT). Summation of recognition and movement reaction time results in a total reaction time (TRT = RRT + MRT [20].Critical Fusion-Flicker Frequency Threshold test by Leeds Battery Instrument

(Zak GmbH.H-D-8346 Simbach/Inn). The subject was asked to concentrated on 4 illuminated sites and to respond when the illuminated site changed from steady state to flickering and when it changed from flickering to steady state mean of 4-5 trials of flicker descending (i.e. from steady to flickering) is called flicker threshold while the mean of flicker ascending (i.e. from flickering to steady) is called fusion threshold, summation of both called critical flickering-fusion frequency threshold (CFFT) [21].

## Statistical analysis

Results are expressed as number, and mean ± SD. The data were analyzed by using Student's "t" test (paired two tailed) taking $p \leq 0.05$ as lowest limit of significance.

**Table 1:** The characteristic of the study

| Number | 20 |
|---|---|
| Gender | |
| Male | **17** |
| Female | **3** |
| Age (year) | **20-21** |
| Range | **1** |
| Mean ± SD | **20.2±0.41** |
| **Drug** | **Desmopressin** |
| **Rout/dose** | **Trans-nasal 10µg/puff(2 puff)** |
| Device | **Leeds battery tester** |
| Statistical analysis | **Student's "t" test** |

## Results

Desmopressin acetate significantly improve psychomotor performances and cognitive functions in all its parameters of Leeds battery tester $p<0.05$ except critical flickering where desmopressin showed insignificant effects $p>0.05$ table (2).The pronounced effects of desmopressin acetate after single trans-nasal dose more appeared on TRT(total reaction time), AVP decreased it from(726.712±21.5) to( 411.511±23.20) $P<0.01$ but insignificant effect on critical flickering ( $p>0.05$ ) figure(1).

**Table 2:** Effects of single trans-nasal desmopressin acetate on psychomotor performances parameters.

| Variables | Before(mse) | After(mse) | *value p* |
|---|---|---|---|
| ➢ TRT | 726.712±21.5 | 411.511±23.20 | ***P<0.01*** |
| ➢ RRT | 345.171±21.31 | 219.119±11.51 | ***P<0.05*** |
| ➢ MRT | 381.097±11.3 | 192.398±23.1 | ***P<0.05*** |
| ➢ C.Flickering | 25.82±2.1 | 21.22±1.8 | ***p>0.05*** |
| ➢ C.Fusion | 32.42±1.2 | 22.35±1.5 | ***p<0.05*** |
| ➢ C.F.F | 58.24±3.3 | 43.57±3.3 | ***p<0.05*** |

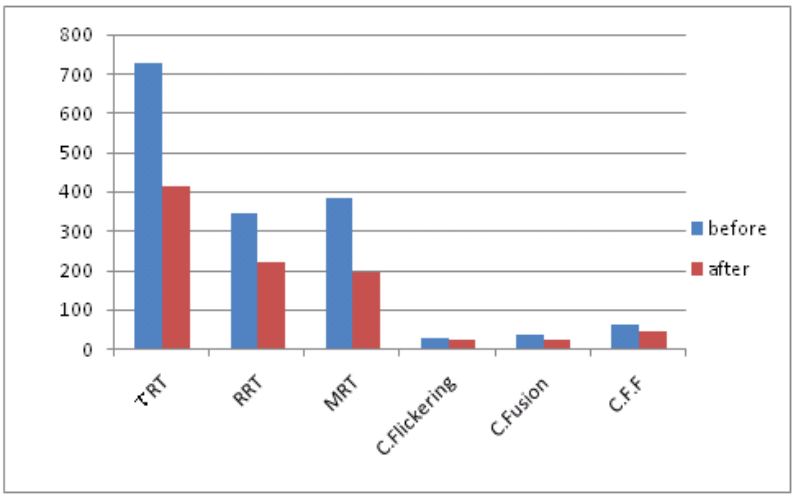


**Figure 1:** Trans-nasal desmopressin effects on psychomotor measures and flickering-fusion frequency

## Discussion

Centrally acting AVP is believed to play an important role in the regulation of learning and memory, social behaviors, circadian rhythmicity and thermoregulation [22,23].

In this study desmopressin used as experimentally new model for selective more acting vasopressin ,this study showed that desmopressin acetate significantly enhanced and accelerate the mental task and cognitive function via amelioration of psychomotor performances events and central processing function through upgrading in critical fusion frequency and to a lesser extend critical flickering frequency but cumulative effects via critical flickering-fusion frequency threshold it produced significant effects $p<0.05$.

Gender differences debarred from this study due to small sample size (20 volunteers 3 female and 17 male); this selection support this study because as mentioned in the introduction vasopressinergic system more efficient in male than females.

Small amounts of unmetabolised desmopressin can pass through the blood-brain barrier (BBB), which cause improvement in mental functions that indicate a nonspecific stimulation of the central nervous system. [24'25].

Mishima *et al*., 2001 and Egashira *et al*., 2004 studies in male rats and mice have suggested that vasopressin acting on the V1aR is important for normal spatial memory and microinjected of vasopressin into the ventral hippocampus of rats can improve scopolamine induced impairment of spatial memory [26'27'28].

In many studies desmopressin, as well as their metabolites have been found to act as potent neurotransmitters in the central nervous system; their effects on behavioral consequences and on memory have been investigated extensively that desmopressin increased short-term memory but middle and long-term memory remained unaffected [29].

Therefore, short-term memory may constitute an indirect measurement of "alertness" of an individual because this arousal system or ascending reticular activating system, has originally been located in the brain stem and their different neurotransmitter; noradrenalin, serotonin, acetylcholine and histamine currently involving the locus coeruleus [30] ,so it might be conceived that the effects of vasopressin could involve an effect on adrenergic nerves leading to release of noradrenalin or alternatively, vasopressin could act with noradrenalin at postjunctional receptor sites, because noradrenalin release was not measured in this study, a contribution of prejunctional facilitating effects cannot be excluded.

The fact that the concentration response curves to vasopressin were not modified by prazosin, an α1-adrenoceptor blocker, this suggests that the action of this peptide does not involve release of noradrenalin via receptor level; the possibility that vasopressin could block the reuptake of noradrenalin and therefore enhance the psychomotor response is unlikely because the potentiating effects were still evident in the presence of cocaine, this suggests that neuronal reuptake of noradrenalin in CNS is of little importance, a circumstance that is mainly dependent on brain region and gender [31].

Dalley *et al*., 2001 study showed that the performance of visuospatial attention tasks is known to be associated with a greater release of noradrenalin within cerebral cortical regions [32].

The facilitating effects of desmopressin may be through stimulation of cholinergic system which have impact on memory or may act as neurotransmitter and stimulate the synthesis of biochemical agents, thus acting as a neuromodulator [33'34].

The impacts of desmopressin on second messenger systems involved in memory processes such as calcium ,calmodulin , protein kinase II , protein kinase a pathways and NMDA receptors in the hippocampus may in part be responsible for desmopressin effects on memory and psychomotor vigilance [35].

Add to this desmopressin exciting choline acetyltransferase activity in visual cortex, stimulating acetylcholine release and inositol – phospholipid metabolism in the hippocampus and cerebral cortex have also been reported to be involved for desmopressin effects on memory processes and cognitive abilities, which reflects improvement in total reaction time and critical-flickering threshold via activation of ascending and descending neural pathway at reticular activating system(RAS) [36].

Moreover; desmopressin -induced nitric oxide production via V2 receptor activation of the phosphoinositide pathway, and because V2 receptor also found in hippocampus and amygdeloid neurons ,so nitric oxide may play an important role in CNS activation and improvement of vigilance and psychomotor performances[37], but unfortunately nitric oxide level not measured in this study .Consequently, any drug whatever its primary action, if it enhances nitric oxide release or scavenging peroxynitrite may provide beneficial effect on cognitive function [38].

Therefore, the beneficial effect of desmopressin on both the fusion-flickering variables and psychomotor performances are possibly related to donating nitric oxide, rather than to its effect on vasopressin/ adrenergic receptors furthermore the sharp increase in AVP result in a decreased subjective feeling of fatigue and an increased sense of arousal and enhance the mediator's memory of vigilance [39].

In conclusion of this study desmopressin acetate produced remarkable effect on human psychomotor and cognitive performances and regarded as new therapeutic modality for CNS activation and improvement of human arousability functions via direct receptor effects and modulation of other neurotransmitters rather than the hormonal effects.

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* *Lecturer in Department of Pharmacology, College of Medicine, Al-Mustansiriya University, P.O. Box 14132, Baghdad, Iraq Email:Hayder_M36@Yahoo.com*